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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/051,034	03/31/1998	IAN FARQUHAR CAMPBELL MCKENZIE	3164.98USWO	7533

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	37

DATE MAILED: 06/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N . 09/051,034	Applicant(s) MCKENZIE ET AL.	
	Examiner Joseph T Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-14,17-24 and 26-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-14,17-24,26-29 and 32-35* is/are rejected.

7)☒ Claim(s) *6 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

File

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

Applicants amendment filed April 1, 2002, paper number 30, has been received and entered. Claims 11 and 15 have been canceled. Claims 1, 8, 9, 17-19, 22-24, 26, 28 and 29 have been amended. Claims 30-35 have been added. Claims 1-10, 12-14, 17-24, and 26-35 are pending and currently under examination.

Claim Objections

Claims 19, 22, and 28 previously objected to for informalities is withdrawn. Amendments to the claims have obviated the basis of the objection.

Claim 6 is objected to for the following informalities: In the Applicants' After Final amendment filed April 2, 2001, paper number 24, and entered upon filing the request for Continued Prosecution of the Application filed July 30, 2001, paper number 27, it is noted that 'secretor sialytransferase' was amended to recite 'secretor, and sialytransferase'. It is noted that some transferases are secretor glycotransferases, however a 'secretor' alone is not a type of glycosyltransferase.

Claim 30 is objected to for the following informalities: as generally supported in the present disclosure GT is the acronym of glycosyltransferase. When not specifically defined in the specification, the first presentation of an abbreviated term should be denoted by setting forth the full name indicating the term to be used subsequently.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12-14, 16-24, and 26-29 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

Upon review of claim amendments and in light of Applicants' arguments Examiner agrees that the present claims do not introduce new matter, and the rejection is withdrawn.

Claims 1-8, 10, 12-14, 16-17-24, and 26, 27, 29 stand rejected and newly added claims 30, 32-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence which encodes a chimeric glycosyltransferase comprising a fucosyltransferase operatively linked to a localization signal of a galactosyltransferase wherein the expression of said chimeric glycosyltransferase in a cell reduces the amount of galα-1,3-gal relative to a cell which does not express said chimeric transferase and methods of use, it does not reasonably provide enablement for the broad scope of any chimeric glycosyltransferase for reducing the galα-1,3-gal HAR antigen encompassed by the present claims The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants review the general nature of glycosyltransferase enzymes and argue that one of skill in the art would know in light of the teachings in the present specification, what domains to use and combine to produce a chimeric glycosyltransferase which is capable of reducing the galα-1,3-gal HAR antigen epitope in a cell of interest. See Applicants' amendment, pages 10-12. Applicants' arguments have been fully considered, but not found persuasive.

In the instant case, enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on

the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

It is noted that claims 9, 28 and 31 recite specific embodiments which are fully enabled by the present disclosure, and the rejection over claims 9, 28 and 31 is withdrawn. Further, it is noted that the present claims have been amended to encompass a nucleic acid which encodes a chimeric glycosyltransferase which has the enzymatic characteristic of reducing the amount of galα-1,3-gal when expressed in a cell. However, the remaining claims broadly encompass the combination of almost any glycosyltransferase catalytic domain and localization signal. The instant invention is based in part on the observation that expression of α-1-2 fucosyltransferase can significantly reduce the amount of galα-1,3-gal by successfully competing with galactosyltransferase for the same substrate. The instant invention provides an improvement to the observation by generating a chimeric enzyme which will be localized to the same location in the cell as the galactosyltransferase to more efficiently compete for substrate. The ability of the

fucosyltransferase to successfully out-compete the galactosyltransferase is based on the unexpected hierarchal relationship of these two enzymes for the same substrate. The present disclosure provides working examples for the successful use of fucosyltransfereases. The declaration provided as an attachment to the after final amendment filed April 2, 2001, paper number 24, provides evidence that other fucosyltransferases besides that instantly disclosed is capable of decreasing the galα-1,3-gal epitope when expressed in a cell. In light of the additional evidence, Examiner would agree that other fucosyltransferases besides those specifically taught in the instant disclosure would function to reduce the amount of galα-1,3-gal epitope present on a cell. Further, in light of the art and evidence of record, Examiner would agree that any localization signal which would direct the presence of the chimeric transferase to the same compartment as the galactosyltransferase would be fully enabled.

However, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In the instant case the success of the instant invention is based on the ability of fucosyltransferases to out-compete galactosyltransferase for substrate and reduce the amount of galα-1,3-gal epitope produced. There is no nexus between this particular class of transferases and other transferases and/or modifying enzymes for the successful reduction of the galα-1,3-gal epitope. Even if one were to concede that expression alone of other transferases could compete for a given substrate, the specification fails to provide the necessary teaching and guidance on what enzymes to use and what particular targeting sequences the artisan should combine to achieve the appropriate chimeric enzyme. Further, fucosyltransferase seems to function by virtue of a hierarchal function over galactosyltransferase, there is no evidence that other enzymes will have a similar property. Lacking any substrate preference, the specification fails to provide the necessary guidance for the levels of expression and the necessary means to achieve the expression levels for each particular enzyme encompassed by the claims.

It is noted that the general methodology used in recombinant DNA technology used to combine catalytic domains with signaling domains is not the basis of the instant rejection. Rather, the high degree of unpredictability associated with the claimed characteristics of the encoded chimeric glycosyltransferase and method of use underscores the need to provide teachings in the specification that would provide the artisan with specific details that achieve the affect claimed. Without guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan. As noted previously, the court has stated that

"patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005).

In addition, it is noted that claims 18-19 and 22 encompass organs or methods of reducing hyperacute rejection-associated epitopes in cells which are interpreted to embrace methods for xenotransplantation comprising *ex vivo* and/or *in vivo* use of nucleic acids for gene therapy use in mammals wherein cells or organs comprising such are programmed to be immunologically acceptable as a consequence of downregulation of carbohydrate epitopes recognized as non-self. The physiological art is recognized as unpredictable (MPEP 2164.03), and at the time of the claimed invention successful use of gene therapy was not routinely obtainable by those skilled in the art at the time the instant application was filed. As summarized by Anderson: "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human diseases [Nature, Vol. 392:(Supp.), 1998, p. 25, first paragraph]...[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. In the instant case the specification provides little or no guidance teaching one of ordinary skill in the art how to use the cells or "expression units" (and methods for their production) covered by claims 19-24 for *ex vivo* gene therapy. Neither the specification, nor Applicants response

addresses the problems and unpredictability in the *in vivo* gene delivery art nor does the specification provide adequate guidance teaching one of ordinary skill in the art how to make and use the claimed invention for either direct *in vivo* delivery of glycosyltransferase expression constructs or use of nucleic acids for producing cells for *ex vivo* or *in situ* gene therapy resulting in cells or tissues "suitable for transplantation."

Thus, for the reasons above and of record, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed, and therefore, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 8, 9, 17, 18, 23, 26, 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

First, it is noted that amendments to the claims have obviated each of the basis of the specific rejections set forth in the previous office action.

Claims 1, 18, 26 and 29 are unclear and indefinite in the recitation of 'the improvement...' because this term does not have adequate antecedent basis in the claim. The claim is unclear because what is being improved is not clearly set forth. It is noted that the claim is directed to a polynucleotide sequence and any intended use provides no patentable weight to the claimed product. Even if the improvement were to be defined prior to the recitation, the claim is indefinite because it depends on when, where and how the polynucleotide is used in order to assess any potential change as an improvement.

Claims 2 and 17 are confusing because in light of the amendments to claim 1 for the localization of chimeric product to the same location of the enzyme with which it would compete, it is unclear how claim 2 further limits claim 1. It is unclear if localization alone, as indicated in claim 1, does not 'enable the catalytic domain to compete' or alternatively, claim 2 is unclear and indefinite because the characteristic imparted by 'said localization signal' is not clearly defined wherein it is differentiated from that described in claim 1.

Claims 3, 18, 19, 23, 26 and 28 are confusing and indefinite because it depends on who the recipient is. It is noted that claim 1 is directed to a polynucleotide, and any intended use of said product does not provide any further limitation to said product. Even if a proper context could be defined and the particular change in glycosylation established, the claim is indefinite because the change may be recognized as foreign in one individual but not another.

Claims 8 is unclear and indefinite in the recitation of 'is from the same cell type as the cell of claim 1'. First, claim 1 is directed to a polynucleotide sequence, not a cell. Further, two

types of cells are described in claim 1, with and without a transgene, and the antecedent basis to which cell 'the cell' refers is unclear. Additionally, the same transferases can be/are expressed in multiple cell types, and thus, the metes and bounds of the claim are unclear because it is unclear if the localization signal obtained from one cell type but present in other cell types would anticipate the claim. Because the same sequence can be obtained from multiple sources the metes and bounds of the claim are unclear because the location from which one obtains the sequences can not be determined by a 'cell type'.

Claim 9 unclear and confusing because the sequence alone is not responsible for producing an epitope that causes hyperacute rejection. Even if the sequence was present in the proper context and expressed at the necessary levels, the sequence would theoretically reduce the amount of gal(1,3)gal epitope, *i.e.* produce gal(1,3)fuc.

Claim 30 is vague and unclear in the recitation of 'GT'. The term GT is not specifically defined in the specification, and a review of the art of record indicates that the term can be used generally for glycosyltransferase or more specifically for particular galatosyltransferases. Amending the claim to more clearly indicated the intended meaning of this term would obviate the basis of the rejection.

Conclusion

No claim is allowed. The claims are free of the art of record because while the over-expression of fucosyltransfereases have been demonstrated to reduce the galα-1,3-gal HAR

antigen, there is no teaching in the art which anticipates nor teachings which provides the motivation to generate the chimeric glycosyltransferases characterized by a particular enzymatic activity encompassed by the present claims. However, the claims are subject to other rejections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630